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Withholding initial vancomycin in febrile neutropenia despite implanted catheters

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Empirical initial meropenem monotherapy allowed withholding of vancomycin in febrile neutropenic children with implanted central venous catheters.

Cancer children with fever and neutropenia are at high risk for bacterial infections and require prompt antimicrobial therapy [3]. Since implanted central venous catheters (ICVC) provide an additional risk for infectious complications [6] and are increasingly used in these children, we evaluated their impact on the need to complement initial empirical carbapenem monotherapy.

During a 24-month period, we prospectively evaluated 41 cancer children aged 0.3 to 15.4 years (mean 5.9 years; median 6.1 years) with ICVC (Port-a-Cath, Pharmacia, Dübendorf, Switzerland) manifesting 82 episodes of fever (axillary temperature $>38.5^{\circ}\text{C}$ once or $>38.0^{\circ}\text{C}$ on ≥ 2 occasions within 12 h) and neutropenia (<500 neutrophils/ μl). A total of 33 episodes occurred in 19 children with acute lymphatic leukaemia, 23 in six with acute myelogenous leukaemia, two in two with lymphoma, and 24 in 14 with solid tumours. Empirical treatment was started with meropenem (20 mg/kg tid). When fever and neutropenia persisted and cultures were negative after 48 h, vancomycin (40 mg/kg per day) and after another 48 h amphotericin B (0.6 to 1.2 mg/kg per day) was added. Antimicrobials were continued for 5 days after defervescence or termination of neutropenia and, if a pathogen was isolated, treatment was continued for 14 days according to susceptibility testing.

Of 82 episodes, 23 (28%) were microbiologically documented, including 18 bacteraemias, two urinary tract and three viral infections (Table 1), 28 (34%) were clinically documented and 31 (38%) were unexplained. Bacteraemia was caused by gram-positive bacteria in 15 (83%) episodes (Table 1); 14 (78%) of these isolates were meropenem-susceptible, as were *Escherichia coli* and *Citrobacter spp.* isolated from urine. No invasive fungal infection was diagnosed. Neutropenic fever persisting >48 h demanded addition of vancomycin in 35 (43%) episodes and after 96 h of amphotericin B in 12% (Table 1). Isolation of meropenem-resistant bacteria demanded vancomycin addition in four (5%) episodes. Since symptoms were not severe and patients did not deteriorate, vancomycin was not given before 48 h, i.e. not before meropenem resistance of the isolate was known. Repeated isolation of the same species from blood in three of four children suggested colonisation of the ICVC and its removal resulted in resolution of fever.

Initial empirical meropenem monotherapy for febrile neutropenia in cancer children with ICVC was effective. The incidence of bacteraemia (22% of episodes) was similar to that in previous reports of children [2, 4, 5]. The high rate of gram-positive bacteraemias (83%) extends the shift towards gram-positive infections [2, 3, 4] and may be influenced by the universal presence of ICVC. Although the catheter frequency in children in previous studies ranged from 82% to 90% [2, 4], its relevance with respect to infections was not investigated.

All meropenem-resistant bacteria isolated from blood (5% of episodes) were gram-positive, susceptible to vancomycin, and caused no life-threatening infections. Three of four resistant isolates grew from contaminated ICVC. Withholding vancomycin until the meropenem resistance of the isolate was known resulted in no disadvantage for the patients. Such a procedure, optional in recent recommendations [3], would allow a vancomycin restriction of up to 100% within the first 48 h. In our cohort this translates to a prevention of vancomycin exposure by 164 days. We added vancomycin after 48 h

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Table 1 Febrile neutropenic episodes ($n = 82$) in 41 cancer children during a 24-month period. Episodes were classified as microbiologically documented (including 18 bacteraemias, two urinary tract and three viral infections), clinically documented (site of infection identified, no organism isolated) and unexplained fever (infection most likely, no site or organism identified)

Episode	N	Meropenem-resistant	Escalation	
			Plus vancomycin	Plus amphotericin B
Microbiologically documented	23	4	16	4
Bacteraemia due to:	18	4/18		
<i>Streptococcus mitis</i>		0/5		
<i>Staphylococcus epidermidis</i>		2/4		
<i>Escherichia coli</i>		0/3		
<i>Streptococcus oralis</i>		0/2		
<i>Staphylococcus aureus</i>		0/1		
<i>Staphylococcus hominis</i>		0/1		
<i>Stomatococcus mucilaginosus</i>		1/1		
<i>Bacillus cereus</i>		0/1		
Clinically documented	28		10	3
Unexplained fever	31		9	3
Total	82	4 (5%)	35 (43%)	10 (12%)

in 43% of episodes which is within the range of 25%–50% reported in other paediatric studies [1, 2, 4].

Although this study was non-comparative, the very low proportion of meropenem-resistant isolates still justifies our conclusion that vancomycin is initially not needed in addition to empirical meropenem treatment in febrile neutropenic cancer children with ICVC. Administration of vancomycin is to be added only following isolation of meropenem-resistant bacteria or on demand by escalation guidelines.

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